REMARKS

Reconsideration of this application is respectfully requested. Claims 1-17 were pending in the application. Claims 1-12 and 14-17 were withdrawn from consideration. Claim 13 was rejected. The amendment proposes to amend claim 13. New claims numbered 18-23 have been added for consideration. Support for the new claims can be found throughout the specification, in particular on page 9, lines 6-30; page 15, lines 7-9, page 19, lines 16-27; page 14, lines 18-25; in Materials and Methods and the Discussion found on pages 10-23; in Example 1 on pages 23-33; and in original claims 8, 10 and 12. If the amendment proposed above is entered, the claims remaining for consideration will be claims 13 and 18-23. No new matter has been added by way of this amendment.

Claim 13 was rejected under 35 U.S.C. 112, second paragraph for being indefinite. Applicant has respectfully traversed the Examiner's rejection, and have amended the claims to better clarify the invention. Support for the amended claims can be found throughout the specification, and more particularly, in original claims 2 and 4. Further support can be found on page 9, lines 6-15 and in Materials and Methods and the Discussion found on pages 10-23; and in Example 1 on pages 23-33. Withdrawal of the rejection is respectfully requested.

Claim 13 was rejected under 35 U.S.C. 112, first paragraph for lack of enablement. In particular, the Examiner alleges that the specification, while being enabling for a method using thymidine kinase (TK) and gancyclovir (GCV) as a therapeutic combination, does not reasonably provide enablement for all therapeutic nucleotide sequences and nucleobase analogs. It is the Examiner's belief that undue experimentation would be required to practice the claimed invention with a reasonable expectation of success. While Applicant respectfully traverses the Examiner's rejection, and assert that one skilled in the art could utilize the teachings of the present invention with a reasonable expectation of success for other nucleoside analogs, Applicant has amended the claims to place the application in condition for allowance. Furthermore, Applicant reserves the right to pursue the broader scope of subject matter in a further continuation application.

Claim 13 was rejected under 35 U.S.C. 112, first paragraph for non-compliance with the written description requirement. In particular, the Examiner alleges that the present application sets forth thymidine kinase (TK) and gancyclovir (GCV) as a combination that is therapeutic, and that the full scope of the claimed invention was not in Applicant's possession at the time of filing.

While Applicant respectfully traverses this rejection, the claims have been amended to place the application in condition for allowance. Furthermore, Applicant reserves the right to pursue the broader scope of subject matter in a further continuation application.

Claim 13 has been rejected under 35 U.S.C. 102(b) as being anticipated by Deliganis et al. (AJNR 18:1401-1406, 1997). Applicant respectfully traverses the Examiner's rejection for the following reasons. Deliganis et al. teach a method to treat tumors comprising administering a retroviral vector with a first nucleic acid sequence being therapeutic (TK) and administering GCV. Applicant has amended the claims to better clarify the invention and as such, assert that the claims as amended are not anticipated by Deliganis et al.. Withdrawal of the rejection is respectfully requested.

Claim 13 has been rejected under 35 U.S.C. 102(b) as being anticipated by Nalbantoglu et al. (Neurology 52: A425,1999). Applicant respectfully traverses the Examiner's rejection for the following reasons. Nalbantoglu et al. teach a method of treating tumors in a mammal comprising a therapeutic nucleic acid sequence (TK) and a nucleobase (GCV). Applicant asserts that this reference is the inventor's own work and that the present application is a National Stage Application filed in the United States under 35 U.S.C.§371, which claims priority under 35 U.S.C. §119 (a)-(d) to PCT application number PCT/CA00/00445, filed April 20, 2000, which claims priority under 35 U.S.C. §119(e) to United States provisional application number 60/130,680, filed April 23, 1999. Because the present application claims priority to United States provisional application number 60/130,680, filed April 23, 1999, this date precedes the date of the published reference by Nalbantoglu et al., which is December 4, 1999. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 USC §112

Claim 13 was rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner asserts that it is not clear what the metes and bounds of "therapeutic [first nucleotide sequence]", nor is it clear what the metes and bounds of "co-dominantly" is. Furthermore, the Examiner asserts that it is not clear what is meant by "nucleobase" and that the term is treated in the present action as meaning a nucleoside analog. In addition, it is not clear what the outcome of "treat" is, nor is it clear what is meant by sequence

encoding a "marker", and that this term is taken to include a selectable marker as in neo gene which can be selected for by G-418 antibiotic in the culture medium. Applicant respectfully traverses the Examiner's rejection, and have amended the claims to better clarify the invention.

In particular, the claim has been amended to delete reference to "therapeutic first nucleotide" sequence and "co-dominantly" and has been replaced with language that better clarifies the components of the first and second nucleotide sequences. Furthermore, the claim has been amended to clarify that the "marker" is in fact a fluorescent reporter protein, and as such, the claim has been amended to recite "marker which comprises green fluorescent protein". Support for this can be found on page 4, lines 14-18 and on page 5, lines 20-24 and on page 32, lines 3-5. The term "treating" has been replaced by "inhibiting" to better clarify that the outcome of "treat" is suppression or inhibition of tumor growth. Support for this amendment is inherent in the text and can be found in Figure 4, which illustrates "growth suppression of human glioma cell lines". Further support can be found on page 12, lines 29-31 under "Growth Suppression Assays", continuing on to page 13, lines 1-11. As the Examiner has correctly pointed out, the term "nucleobase" is treated in this action as meaning a nucleoside analog, which is known to those skilled in the art, and as such, the claim has been amended to recite "nucleoside analog". Applicant asserts that the amendments to claim 13 render the rejections under 35 U.S.C. 112 for being indefinite moot. Withdrawal of the rejection is respectfully requested.

Claim 13 was rejected under 35 U.S.C. 112, first paragraph for lack of enablement. In particular, the Examiner alleges that the specification, while being enabling for a method using thymidine kinase (TK) and gancyclovir (GCV) as a therapeutic combination, does not reasonably provide enablement for all therapeutic nucleotide sequences and nucleobase analogs. The Examiner alleges that undue experimentation would be required to practice the claimed invention with a reasonable expectation of success. While Applicant respectfully traverses the Examiner's rejection, and assert that one skilled in the art could utilize the teachings of the present invention with a reasonable expectation of success for other nucleobase analogs, Applicant has amended the claims to place the application in condition for allowance. In particular, claim 13 has been amended to recite:

"...wherein said second nucleotide sequence comprises a suicide gene, wherein said suicide gene is thymidine kinase..."

Claim 13 has been further amended to recite:

"... administering to said mammal a non-toxic nucleoside analog, wherein said nucleoside analog is gancyclovir."

Accordingly, based on the amendment to claim 13, withdrawal of the rejection is respectfully requested. Furthermore, Applicant reserves the right to pursue the broader scope of subject matter in a further continuation application.

Claim 13 was rejected under 35 U.S.C. 112, for non-compliance with the written description requirement. In particular, the Examiner alleges that the present application only sets forth the written description for thymidine kinase (TK) and gancyclovir (GCV). Applicant respectfully traverses the Examiner's rejection and has amended the claim to place the application in condition for allowance. Accordingly, claim 13 reads on thymidine kinase and gancyclovir, as noted above.

Accordingly, based on the amendment to claim 13, withdrawal of the rejection is respectfully requested. Furthermore, Applicant reserves the right to pursue the broader scope of subject matter in a further continuation application.

Rejections Under 35 USC §102(b)

Claim 13 was rejected under 35 U.S.C. 102(b) as being anticipated by Deliganis et al. (AJNR 18:1401-1406, 1997). Applicant respectfully traverses the Examiner's rejection and has amended the claims to better clarify the present invention, and as such, asserts that the claims as amended are not anticipated by Deliganis et al..

For example, Deliganis et al. teach a method to treat tumors comprising administering **cells** that were genetically engineered to release retroviral vectors containing the herpes virus thymidine kinase gene and administering GCV. In addition, Deliganis et al. teach that the vector carried by these cells encodes **only the TK gene**. That is, Deliganis et al. is silent on a second nucleic acid sequence encoding a marker such as green fluorescent protein (GFP).

The present invention discloses and claims a method of inhibiting tumor growth by administering a tumor specific **bicistronic retroviral expression vector** comprising **two** nucleotide sequences, one encoding a suicide gene such as thymidine kinase, and the second encoding a reporter (marker) protein such as green fluorescent protein (GFP). These two nucleic

acid sequences are expressed following administration of the expression vector and a nucleoside analog such as GCV. As noted in the present application, the marker sequence *e.g.* green fluorescent protein, allows the clinician to visualize the cells that have been transformed by the expression vector and that are expressing the suicide gene. Deliganis et al. **does not** disclose **two nucleic acid sequences** such as that disclosed and claimed in the instant application. Furthermore, as Applicant notes in the present invention on page 23, lines 7-9:

> *"This constitutes the first report of in vivo delivery of a* ***cell-free*** *retrovector concentrate with tumor-specific, high efficiency gene transfer and expression, with evident biologically significant anti-tumor activity."*

Claim 13 of the present invention, as currently amended, clearly reads on a **bicistronic** vector encoding two nucleic acid sequences, one for the suicide gene (TK) and the second for the marker protein, such as GFP.

Applicant asserts that the amendments and arguments provided to the Examiner obviate this rejection. Thus, Applicant respectfully requests withdrawal of this rejection.

Claim 13 was rejected under 35 U.S.C. 102(b) as being anticipated by Nalbantoglu et al. (Neurology 52: A425, 1999). Applicant respectfully traverses the Examiner's rejection for the following reasons.

Nalbantoglu et al. teach a method of treating tumors in a mammal comprising a therapeutic nucleic acid sequence (TK) and a nucleobase (GCV). Applicant asserts that this reference is the inventor's own work and that the present application is a National Stage Application filed in the United States under 35 U.S.C.§371, which claims priority under 35 U.S.C. §119 (a)-(d) to PCT application number PCT/CA00/00445, filed April 20, 2000, which claims priority under 35 U.S.C. §119(e) to United States provisional application number 60/130,680, filed April 23, 1999. Applicant asserts that the rejection under 35 U.S.C. 102(b) is improper because the present application claims priority to United States provisional application number 60/130,680, filed April 23, 1999, and this date precedes the date of the published reference by Nalbantoglu et al., which is December 4, 1999. Accordingly, withdrawal of this rejection is respectfully requested.

Fees

A check in the amount of $215 is enclosed to cover the Petition for a Two Month Extension of Time. No other fees are believe to be necessitated by this response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicant asserts that the outstanding rejections based on 35 U.S.C. §112 and 35 U.S.C. § 102(b) have been overcome by the claim amendments presented above. Thus, reconsideration and withdrawal of the outstanding grounds of rejection, and allowance of the claims is believed to be in order and is courteously solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned at the number listed below, so that prosecution of the application may be expedited.

Respectfully submitted,

Veronica Mallon

Veronica Mallon, Ph.D.
Agent for Applicant(s)
Registration No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07601
(201) 487-5800